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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/306,333	05/06/99	VIJG	J

EXAMINER	
SOUAYA,J	
ART UNIT	**PAPER NUMBER**
1655	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/306,333	Applicant(s) Jan Vijg
	Examiner Jehanne Souaya	Group Art Unit 1655

☒ Responsive to communication(s) filed on *May 6, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Sequence Listing

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

2. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims, as well as the entire specification, are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

A) Claim 1 is indefinite because the claim fails to include a positive process step relating back to the preamble. The preamble states "a method for enabling BRCAI and hMLHI gene testing..." but the final step is "providing in such test kit appropriate buffer and gel and solvent materials for use in electrophoresis in orthogonal dimensions for producing spot patterns indicative of gene sequence variations and/or mutations". Therefore it is unclear whether the claim is drawn to a method or to a kit.

B) Claim 1 is indefinite in the recitation of "a method for enabling" as it is unclear how this method is different from a method for BRCAI and hMLHI gene testing, ie, it has not been made clear what part of the method enables gene testing of BRCAI and hMLHI. Applicant's can easily overcome this rejection by amending the claim to read " a method for testing for BRCAI and hMLHI gene sequence...".

C) Claim 1 is indefinite in the recitation of "gene sequence variation and/or mutations..." as it is unclear what a gene sequence variation is which is NOT a mutation. For example, is it a variation in the nucleotide sequence different from wildtype, or does it refer to differential splicing of an mRNA transcript?

D) Claim 1 lacks sufficient antecedent basis in the term "such test kit" as it is unclear what test kit is being referred to, particularly since the preamble of the claim is drawn to a method.

E) Claim 2 is indefinite in the recitation "combined mixtures of the multiplex groups of BRCAI and MLHI" as "the multiplex groups" lacks sufficient antecedent basis. Furthermore, it is unclear what "combined mixtures" are being referred to, for example are they mixtures of the BRCAI and hMLHI nucleotide sequences, or are they mixtures of primers to each gene sequence, or are they mixtures of reagents for use in a test kit?

F) Claim 2 is indefinite in the recitation of "to be subjected to the electrophoresis simultaneously together" as it is unclear whether the PCR products are to be subjected to electrophoresis on the same gel, at the same time?

G) Claim 3 is indefinite in the recitation of "the method of claims wherein" as it is unclear from which claim, claim is dependent.

H) Claim 4 is indefinite in the recitation of "test kits.... prepared by the method of claim 3" as it is unclear what method step is included in claim 3.

NOTE: The examiner stresses the indefiniteness of ALL of the claims, and particularly whether the claims are drawn to methods or to kits. For example, claim 4 is drawn to a kit prepared by the method of claim 3, but claim 3 does not appear to be drawn to a method, but rather to PCR primers.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vijg, Jan (WO 96/39535) in view of Vijg et al (Vijg II, US Patent 6,007,231), Park et al (US Patent 5,948,697) and Liskay et al (US Patent 5,922,855) .

With regard to the interpretation of claims 1-4, the examiner calls to the applicant's attention, the numerous rejections made under 35 USC 112, 2nd paragraph as to the general vagueness and indefiniteness of the claims, which made it difficult for the examiner to determine the scope of the claims. From analyzing the claims, and using the specification for clarification, the examiner submits that the claims appear to be drawn to a method for detecting mutations in the BRCAI and hMLHI genes comprising providing PCR primers capable of amplifying the entire coding sequence of the BRCAI and hMLHI genes, amplifying a test sample containing nucleotide sequences by PCR with these primers producing a first set of amplification products, subjecting this first set of amplification products to short distance multiplex PCR providing a second set of amplification products (note, it is unclear what primers are used for this short distance PCR), and subjecting the second set of amplification products to two dimensional gel electrophoresis to

produce a characteristic spot pattern for a specific mutation in either the BRCAI or the hMLHI gene.

Vijg teaches a method for diagnostic testing of DNA using PCR amplification followed by electrophoretic separation of the resulting fragments to detect possible gene variants of mutational defects (see abstract), specifically in the retinoblastoma gene. Vijg teaches that with the method, it is possible to test individual at any time for inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases (see p. 3, lines 1-8). The method taught by Vijg comprises amplifying regions of target DNA, usually protein coding regions (exons), by PCR (see p. 6, lines 20-23) using primers which have been positioned to cover the exons. Vijg teaches that these amplification reactions are conducted separately, eg., if 27 exons in a gene are being analyzed, then 27 separate PCR reactions must be conducted, but also teaches that it is usually possible to conduct a few PCR reactions together in one tube (see p. 7, first para). Vijg then teaches that primers for short PCR are positioned such that a) the desired target sequences should be covered by amplicons of between 100 and 600 bp, b) amplicons should have optimal melting behavior, ie: consist of one lowest melting domain in addition to the GC-clamp attached to one of the primers, c) optimal amplicon distribution over a 2D gel, and d) similar reaction kinetics (See table 1, p. 13). Vijg then teaches that the PCR conditions are set up separately for each primer set with the long-PCR products as template for the short PCR and that multiplex co-amplification conditions are developed by grouping primer sets and adjusting

reaction components. After the PCR, Vijg teaches that the mixture of fragments are subjected to 2-D electrophoresis in a denaturing gradient gel(see p. 16, lines 16-20).

Although Vijg does not teach testing gene sequences of the BRCAI gene and hMLHI gene, Vijg does teach the use of the method to generally detect sequence mutations in any gene, provided the nucleotide sequence of the gene is known, and specifically teaches analyzing the retinoblastoma gene. The BRCAI gene and the hMLHI gene sequence were well known in the art at the time of the invention, as was the link between mutations in these genes in different types of cancer (hMLHI in ovarian cancer cell lines, as well as hereditary non-polyposis colorectal cancer, BRCAI in breast and ovarian cancer). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Vijg to detect mutations in the BRCAI and hMLHI gene as Vijg teaches the usefulness of the method in detecting inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases. The ordinary artisan would have been motivated to use the method taught by Vijg to detect mutations in BRCAI and hMLHI as both Liskay et al and Park et al teach mutations in the hMLHI and BRCAI genes and their link to cancer. The ordinary artisan would have had a reasonable expectation of success that using the method taught by Vijg, primers could be generated that would successfully amplify the necessary coding regions of both the BRCAI and hMLHI genes and provide characteristic 2-D spot patterns for certain mutations as Vijg and Vijg II both teach in extensive detail (see pp 7-10, 18-19 of Vijg; and col.2, col.6,

col.9, and claim 1 of Vijg II) how to prepare primers that would be successful in the method taught by Vijg given a known gene sequence.

NOTE: A showing of unexpected results in using the primers of the disclosed invention which gave better results (in the claimed method) than other primers also generated based on the teaching and methods of Vijg and Vijg II, could aid applicant in overcoming the rejection made under 35 USC 103 (a). In other words, Vijg and Vijg II teach methods of generating primers, a showing that the claimed primers gave better results, which were not expected given the teaching of Vijg on how to design primers based on a known sequence, could overcome the obviousness rejection.

5. No claims are allowable over the prior art.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Thursday from 7:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Jehanne Souaya
May 1, 2000

Lisa B. Arthur
LISA B. ARTHUR
PRIMARY EXAMINER
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